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1992 American Society of Human Genetics Presidential Address: Back to the Future

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Genetics has always appealed to me because of its pervasive relevance to all aspects of human biology. I entered the field when it was still possible to make contributions to many different areas, and, with these thoughts in mind, I would like to emulate a recent series of movies dealing with time travel and invite you to join me on four quick trips "back to the future." Our first trip will take us back 30 years to the jungles of the Amazon to answer the following question.

What Do Studies of Brazilian Indians Have to Do with Unstable Trinucleotide Repeats?

I began my formal training in genetics when I entered Oliver Smithies's laboratory at the University of Wisconsin in 1961, as his first postdoctoral student. Oliver had just found biochemical evidence that an allele in the haptoglobin system, Hp^2, was the product of a partial gene duplication involving two other common alleles, Hp^{1F} and Hp^{1S} (Smithies et al. 1962). The hp 1F and hp 1S polypeptides differed by a single amino acid substitution, while the hp 2 polypeptide was nearly twice as large and contained both of the unique substitutions found in the two Hp^1 alleles. Smithies showed how all of his findings could be explained by assuming that the Hp^2 allele had arisen by a breakage and reunion between the end of an Hp^{1F} allele and the beginning of the Hp^{1S} allele. Although gene duplication had previously been invoked by Ingram (1961) to account for the evolution of the globin genes, in retrospect, Smithies's discovery represented the first example of a tandemly duplicated gene sequence in man. It had been known for many years that in *Drosophila* unequal but homologous crossing-over in regions of gene duplication can lead to further expansion or contraction of a duplication complex. It was, therefore, possible to predict the existence not only of triplications (which had in fact already been observed) but also the presence of two distinguishable variants of the Hp^2 allele. These variants, designated "Hp^{2FF}" and "Hp^{2SS}," might be expected to arise from intragenic recombination in Hp 2-1F and Hp 2-1S heterozygotes, respectively (fig. 1). As part of my thesis work, I set about looking for these predicted variants. I had the good fortune to have access to serum samples from more than 1,000 large nuclear families that were being very carefully collected by Newton Morton and his colleagues in northeastern Brazil. It wasn't long before we found the predicted Hp^2 variants (Nance and Smithies 1963). As shown in figure 2, we ultimately identified 12 of the 15 possible genotypes in this five-allele system. Of particular interest to me (table 1) was the fact that there appeared to be a correlation, in different racial subgroups, between which of the two Hp^1 alleles had the highest frequency and which derived Hp^2 variant was the most common. The observed pattern was exactly what you would expect if unequal crossing-over was a relatively frequent event and the mode of origin of the variant Hp^2 alleles was as shown in figure 1. In whites and mestizos, the Hp^{1S} and derived Hp^{2SS} alleles were the most common, while in blacks the reverse was true, and Hp^{1F} and Hp^{2FF} were the most common. Although the trend did not reach statistical significance, I interpreted this observation as suggesting that unequal crossing-over might well be a relatively frequent occurrence and might account for the origin of the variant Hp^2 alleles. De novo events within a family could of course lead to apparent single-locus genetic exclusions of either the mother or the father that would not be confirmed by genetic inconsistencies in other systems. Among 4,443 tested children, 36 parental exclusions were detected in the haptoglobin system. Of these, 12 were freely acknowledged by the parents, and, among the remaining

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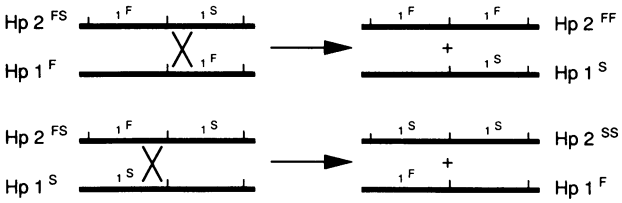


Figure 1 Postulated origin of Hp^{2FF} and Hp^{2SS} alleles from unequal but homologous recombination in Hp2-1F and Hp2-1S heterozygotes.

24, 8 were discrepant only in the haptoglobin system. In seven of these, the observed genetic inconsistency could have been explained by unequal but homologous crossing-over. In four of the seven, either parent could have been excluded. In the remaining three, the father was excluded, but in no case was there clear evidence for a maternity exclusion. Thus, we found no unambiguous de novo example of unequal crossing-over in our family data (Nance 1967). Including rare variants such as Hp^{2M}, Hp^{1Ca}, Hp^{2X}, and Hp^{1U}, a total of nine alleles, more than 20 genotypes, and more than 120 distinct mating types were encountered in the population sample. My work on the haptoglobin system so greatly impressed me with the incredible degree of variability that can arise from regions of genetic duplication that in 1963 I wrote an article, in an obscure journal called *Science,* in which I attempted to account for many of the thalassemia syndromes in terms of alleles that might be expected to arise from unequal crossing-over at the globin duplication complex (Nance 1963). At that time, the persistence of deleterious genes in the population was generally attributed to either recurrent mutation or heterozygote advantage, with sickle cell anemia being the best-known example of the latter (Allison 1954). However, as a clinician, it seemed to me that many genetic diseases with no obvious selective advantage were simply too frequent in the population to be readily explained by conventional mutations. As an alternative, I wondered whether the maintenance of at least some of these disorders in the population might be attributable to the instability of regions of genetic duplication (Nance 1963). Collectively, I suggested that "we may identify this abstract decrease in mean population fitness as the duplication load, a previously unrecognized and possibly important component of the total genetic load" (Nance 1963, p. 125).

In 1963, little was known about the α-globin locus except that it was unlinked to the β-γ-δ complex. In my article I wrote that "although I do not deny that duplication at the α chain locus is a possibility, there is as yet no evidence of it. Consequently, the present hypothesis postulates no duplication, deficiency or fusion alleles at the α locus" (Nance 1963, p. 127).

In retrospect, of course, unequal crossing-over has been documented at the α-, β-, δ-, γ-, and even the ζ-globin loci, leading to deletions, fusion genes, triplications, and even quadruplications, many of which are in fact associated with thalassemia syndromes (Weatherall et al. 1989). I also predicted the existence of anti-Lepore hemoglobins and considered the possibility that genetic duplication might result in somatic instability involving sister-chromatid exchanges or even single-

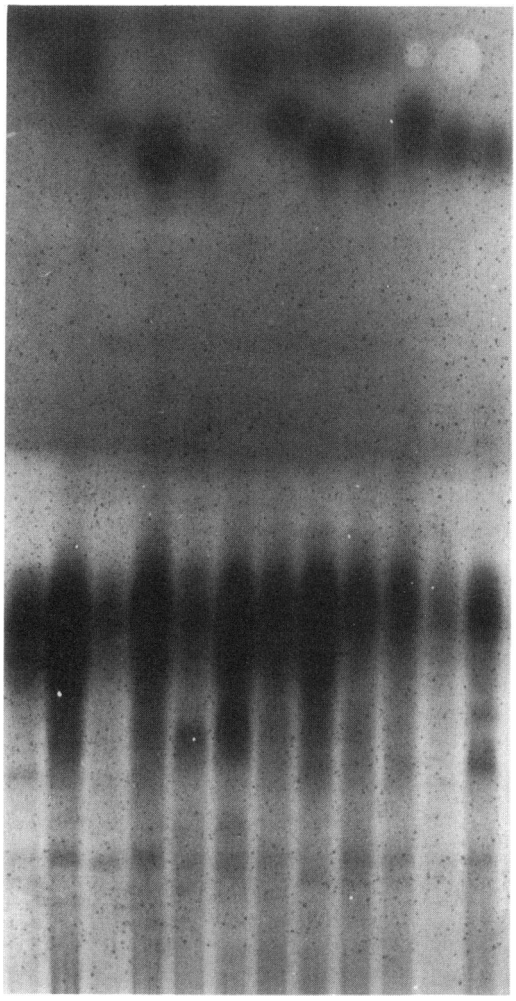


Figure 2 Acidic 8-M urea starch gel showing haptoglobin phenotypes. The lanes, from the left, are Hp1F-1F, Hp1F-1S, Hp1F-2FF, Hp1F-2(FS), Hp1F-2SS, Hp1S-1S, Hp1S-2FF, Hp1S-2(FS), Hp1S-2SS, Hp2FF-2(FS), Hp2(FS)-2(FS), and Hp2(FS)-2SS.

Table 1

Frequency of Hp^2 Variants in Different Ethnic Groups

Allele	Black	White	Mestizo
Hp^{2FF}	.008	.010	.005
Hp^{1F}	.292	.110	.217
Hp^{2SS}	.004	.014	.014
HP^{1S}	.243	.250	.269

strand recombination leading to duplications or deletions of one or more linked genes. In the intervening years, many specific examples of abnormal alleles that appear to have arisen by unequal crossing-over have been documented at the molecular level, and it is now clear that the instability of regions of genetic duplication is not limited to meiotic events or to their tendency to undergo conventional unequal crossing-over. Thus, the variable molecular phenotype that is seen in the fragile X syndrome is thought to reflect the somatic instability of the amplified repeat, and changes in the size of the repeat are not invariably accompanied by the recombination of external markers. Finally, if I were to write an article on the concept of the duplication load today, or if I had known how to come back from the future in 1963, I would certainly have included the diseases shown in table 2 as components of the duplication load. In addition to the three classic examples of unstable trinucleotide repeats (Huntington disease now represents a fourth), several other potential candidates are being reported at this meeting (Li et al. 1992; Riggins et al. 1992). We now know that many duplications and deletions in the Duchenne-Becker gene appear to have arisen from unequal crossing-over (Hu et al. 1988) which has involved sister chromatids in at least some cases (Hu et al. 1989). Other possible examples in addition to the globin loci would include the color-vision (Jorgensen et al. 1990), T-cell receptor (Buresi et al. 1989), and Lp(a) loci (Kamboh et al. 1991), where polymorphic variation exists with respect to the number and structure of the duplicated segments. In the case of the trinucleotide repeat syndromes, hemophilia (Gitschier 1988) and hypoxanthine phosphoribosyl-transferase (Monnat et al. 1992), both the meiotic and/or somatic instability of regions of genetic duplication have clearly been documented. Finally, a growing number of loci exhibit recurrent deletions or duplications that appear to involve recombination within repetitive elements such as *alu* sequences (Lehrman et al. 1987; Sun et al. 1992). Our next trip back to the future begins 25 years ago, where we will learn the answer to another question.

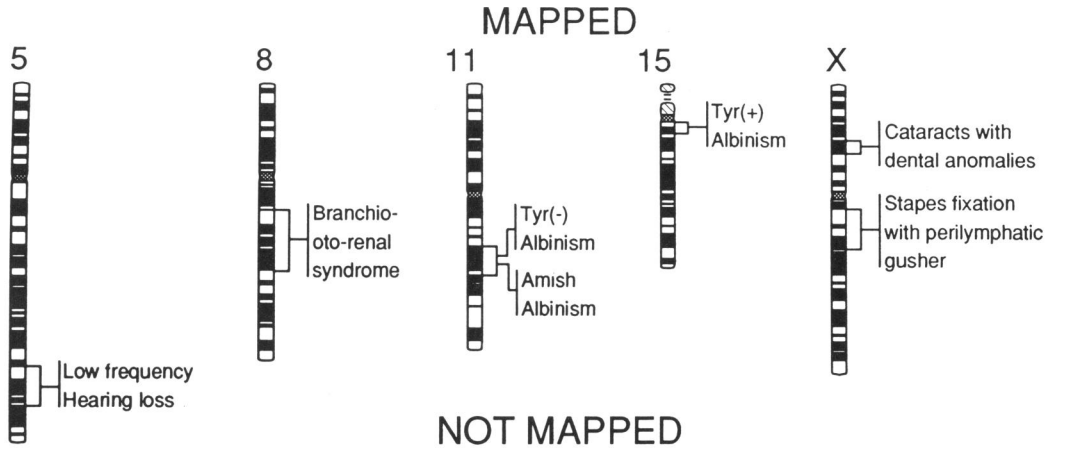
What Do Circus Performers Have to Do with the Human Genome Project?

The decades of the 1960s and 1970s were an era of syndrome delineation, a time when it sometimes seemed as if every patient you saw in the clinic repre-

Table 2

Examples of Loci That Contribute to the Duplication Load

Disease or Locus	Finding(s)
Fragile X	Unstable trinucleotide repeat
Myotonic dystrophy	Unstable trinucleotide repeat
Kennedy disease	Unstable trinucleotide repeat
Alpha-thalassemia	Deletions, triplications, quadruplications
Beta-delta-thalassemia	Fusion genes, anti-Lepore
Gamma-thalassemia	Polymorphic triplications, hybrid genes
Zeta-thalassemia	Polymorphic triplications, quadruplication
T-cell receptor	Polymorphic duplications
Hemophilia	Unstable intragenic duplication
Color-vision defects	Polymorphic duplication, fusion genes
Lp(a)	Polymorphic duplications in coding regions
Duchenne dystrophy	Internal deletions and duplications
Becker dystrophy	Unequal sister-strand crossing-over
HPRT deficiency	Unstable intragenic duplications
LDL receptor	Deletions, duplications, *alu* repeats
Steroid sulfatase deficiency	Recurrent deletions
GM1 gangliosidosis	Internal tandem duplication



MIM#	CONDITION	MIM#	CONDITION
•124800	Progressive, abrupt high frequency hearing loss	•213900	Cerebral sclerosis
•158300	Trismus, pseudocampodactyly syndrome	•215150	Otospondylomegaepiphyseal dysplasia
•202200	Adrenal unresponsiveness to ACTH	•221500	Congenital moderate sensorineural deafness

Figure 3 Partial ideogram showing chromosomal localization of seven syndromes whose genes have been cloned or regionally mapped

sented a new genetic entity or a variant of a recognized syndrome. Figure 3 shows a personal linkage map consisting of genetic conditions I helped describe that have subsequently been localized by other investigators. So far, the map includes only five chromosomes, but several entities remain unmapped, so the total could rise. The loci for X-linked stapes fixation (Nance et al. 1971) and X-linked cataracts (Nance et al. 1974) have been regionally mapped by Brunner and colleagues (Brunner et al. 1988) and by Lewis and his colleagues (Lewis et al. 1990). Similarly, dominantly inherited low-frequency hearing loss (Vanderbilt University Hereditary Deafness Study Group 1968) has been assigned to chromosome 5q31 by Leon and his colleagues (Leon et al. 1992), and the branchio-oto-renal syndrome (Melnick et al. 1976) to chromosome 8q by Haan and colleagues (Haan et al. 1989). Among conditions not yet mapped are the dominantly inherited trismus pseudocampodactyly syndrome (Wilson et al. 1969), which was independently described by Hecht and Beals (1969) at the same meeting, and a curious form of recessive chondrodystrophy that shows thin hair (similar to hair cartilage hypoplasia) and cleft palate with calcification of the ears (similar to diastrophic dysplasia) (Nance and Sweeney 1971). Now that we are learning what extremely different phenotypes can result from genetic defects at the same locus, it will be interesting to see whether the splitters or the lumpers have the last laugh when the molecular basis of the recessive chondrodystrophies is delineated. For many years, the proband in our chondrodystrophy family worked as a barker in the sideshow of a circus, where he met and eventually married the "alligator lady," a woman who had a recessive form of ichytheosis. Their only child was a completely normal female, providing evidence that these two recessive traits are nonallelic, in case there was any doubt. Carl Witkop and I used exactly the same kind of evidence to show that the tyrosinase-positive and -negative forms of albinism are nonallelic in a marriage between two albinotic African-Americans that produced a normally pigmented child (Nance et al. 1971). When I later collaborated with Carl in the description of an unusual form of albinism in the Amish (Nance et al. 1970), I never dreamed I would see the day when its molecular basis would be delineated as it has been by Spritz and his colleagues (Giebel et al. 1991). For those who fear that when the human genome has been sequenced all of the interesting questions will have been answered, I in-

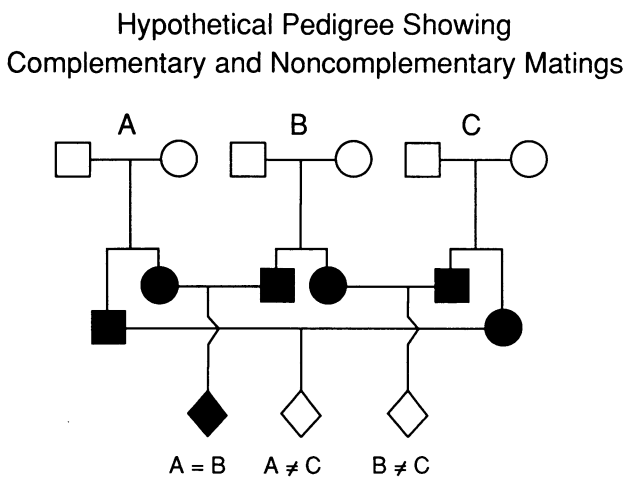


Figure 4 Complementation mapping showing how the identity or nonidentity of different forms of nonsyndromic recessive deafness can be established through an analysis of marriages among the deaf.

vite you to tell me precisely why it is that the gene defect in Amish albinism, a presumed interference with the normal folding of the tyrosinase polypeptide by the substitution of proline for leucine at codon 81, results in complete albinism at birth, with yellow hair and only moderated photophobia in later life. Or, if that question is too easy, why it is that so many nonallelic mutations for albinism are associated with abnormal decussation of neural pathways in the central nervous system (Guillery 1974). The tyrosinase locus, of course, is located on chromosome 11q14, and Ramsay and colleagues (Ramsay et al. 1992) have recently shown that at least one form of tyrosinase-positive albinism is located on 15q, where it may contribute to the hypopigmentation seen in the Prader-Willi phenotype.

As shown by these examples, marriages between affected individuals with recessive traits can provide a very powerful approach to the resolution of genetic heterogeneity. The problem is that, for most phenotypes, marriages of this type are extremely rare. In this country, however, linguistic homogamy constitutes an important exception to this rule, and the resulting marriages among deaf individuals who communicate manually include many complementary and noncomplementary matings between individuals with recessive deafness (Nance et al. 1977). Noncomplementary matings refer to marriages between couples with the same type of recessive deafness who can only produce deaf offspring. In contrast, the complementary matings between partners with different forms of recessive deafness are expected to produce all hearing offspring (fig. 4). The frequency of these marriages raises the possibility that the collection and analysis of marker data from the parents of noncomplementary deaf × deaf matings might constitute a useful strategy for mapping these genes. The method depends upon the reasonable assumption that disequilibrium exists between recessive genes for deafness and very closely linked molecular markers. By definition, the parents in noncomplementary matings have sampled four genes from the population of alleles that cause a particular form of recessive deafness along with their closely linked markers. Under these circumstances, we can ask what are the chances of getting two of a kind, three of a kind, or four of a kind at the marker locus, in comparison with a sample drawn from the general population? We have all heard of Monte Carlo methods in human genetics, and tetrad analysis might well be thought of as the "stud poker" approach to genetic linkage. To test this idea, I used the genes which cause PKU, as a surrogate for recessive deafness (table 3). Note that haplotype 3 is more than 10 times as frequent among the hypothetical sample of deafness alleles, while haplotype 5 is more than 15 times as frequent among normal alleles, indicating that there is substantial linkage disequilibrium at the locus. This means that, among couples with the type of recessive deafness determined by genes at the simulated locus, tetrads containing two, three, or four of the third haplotype should occur more than 100, 1,000, and 10,000 times as often, respectively, as would be expected in the general population. With pooling of rare outcomes, the expected distributions of tetrads for the "deafness" alleles, in comparison with the normal distribution, is shown in table 4. Recessive deafness is known to be genetically heterogeneous. However, even

Table 3

Tetrad Mapping of Recessive Deafness: Assumed Haplotype Frequencies

Haplotype	General Population	Chromosomes with Deafness Allele
1	.350	.181
2	.045	.197
3	.030	.381
4	.318	.136
5	.242	.015
6	.015	.090

NOTE.—Data are from Scriver et al. (1989), with pooling of rare haplotypes.

Table 4

Distribution of Haplotype Tetrads for Markers Closely Linked to a Recessive Deafness Locus 45, in Couples with That Form of Deafness and in the General Population

Haplotype	Proportion of Tetrads with Two,[a] Three, or Four Identical Haplotypes	
	General Population	Deaf Couples
1	.317	.111
2	.008	.128
3	.004	.404
4	.268	.067
5	.169	.001
6	.001	.031

[a] Includes only p^2qr tetrads (i.e., p^2q^2 excluded).

if any particular form of recessive deafness accounts for only a small fraction of the total, it will produce a detectable distortion in the tetrad distribution. For example, if recessive deafness is assumed to be composed of equally frequent phenotypes produced by single pairs of major genes at as many as 20 unlinked loci, a sample of 400 noncomplementary matings would appear to be sufficient to detect a significant difference between the observed and expected distribution of tetrads at the simulated locus (table 5). Now that I have learned how to come back from the future, I am pleased to predict that tetrad analysis of noncomplementary matings among the deaf will prove to be one of the most effective strategies for mapping recessive loci for nonsyndromic deafness. Our next trip will take us farther back in time, to a small hospital in Tennessee in 1956, where we will seek an answer to yet another question.

What Does the Delivery of Twins Have to Do with Genomic Imprinting?

The study of twins is a research interest of mine that began when, as an extern during my second year in medical school, I helped deliver a pair of twins and innocently asked the attending physician, Dr. William W. Pugh, who was a close friend of my family, how you could tell if they were identical or fraternal. "You Harvard students are all the same," he fumed in his high-pitched Cajun wail. "Why don't you find out for yourself?" That incident led to a prize-winning student paper on twins which was later published in *Medicine* (Nance 1959) and began a career-long fascination with these remarkable experiments of nature. In 1975, Linda Corey and I described a then-new research design involving the analysis of data from the families of MZ twins, which capitalized upon the multiple unique social and biologic relationships that exist within these MZ-twin half-sibships (Nance and Corey 1976). In particular, by contrasting the similarities of the half-sib offspring of male and female MZ twins, we can search for differences in the effects of genes derived from the mother and father, respectively. In 1983, my colleagues and I applied this research design to the analysis of data on the birthweights of 1,694 offspring of 395 MZ twin pairs and found that the pooled maternal half-sib correlation (.309) was almost as large as the full-sib correlation (.476), while the paternal half-sib correlation was not significantly different from zero (−.031). This pattern of covariation strongly suggests that the maternal—rather than the paternal—genes are responsible for genetic variation in birthweight. However, in 1983, no genetic mechanism was known which could explain how the parental origin of a gene could influence its expression, so we interpreted our data as indicating that as much as 39% of variation in human birthweight arises from genetic or environmental maternal effects that are common to MZ female twins, 15% to environmental factors that are unique to individual mothers, and 46% to environmental differences that are unique to individual pregnancies (Nance et al. 1983). Now that we are back in the future, of course, we know that genomic imprinting is a mechanism that can result in profound differences in the phenotypic effects of genes that are inherited from the mother and father, and genomic imprinting could lead to exactly

Table 5

Tetrad Analysis of Recessive Deafness: Power Analysis

No. of Loci and No. of Couples	χ^2
20:	
400	35.33*
200	12.57
100	.87
10:	
400	162.24*
200	69.70*
100	25.13*
5:	
400	704.27*
200	324.70*
100	141.62*

* $P < .01$.

the same pattern of correlations that we did in fact observe. It is of considerable interest that many of the genes and chromosomal regions that have been shown to exhibit imprinting have phenotypic effects on body size (Surani et al. 1988; Leff et al. 1992), and it will be of great interest to determine the extent to which genomic imprinting at these loci can in fact account for the maternal effects that we observed.

Another topic that I would like to discuss is the interpretation of twin concordance data. Subject to the usual caveats about possible intrauterine and special twin environment effects, traits that exhibit a high MZ concordance rate have generally been assumed to be genetic in origin. Unfortunately, I think the converse has also been tacitly assumed for traits that exhibit a low concordance rate—namely, that, since these conditions are "obviously not genetic," they must be attributable to some definable cause in the external environment. A number of years ago a committee of the National Academy estimated that no more than about 10% of human cancers are attributable to genetic causes and concluded that factors in the external environment, such as diet or exposure to carcinogens, were responsible for the remainder. I have often suspected that this estimate must have been influenced by twin concordance data. If only 5%–15% of MZ twins are concordant for cancer, how could genetic factors possibly be of any greater importance? However, knowing what we now do about the role of somatic mutation in the etiology of retinoblastoma, for example, we could confidently predict that, even in the case of familial retinoblastoma, the concordance rate for MZ twins would not be 100%, but only about 85%. No one would now interpret this result as indicating that the cancer in the discordant pairs arose from a nongenetic cause. In a similar manner, considerable interest has recently been directed towards the phenotypic expression of X-linked traits in MZ female twins. Dating as far back as 1912, female MZ twins have been documented who were discordant for a variety of X-linked traits, including two of the five Dionne quintuplets, who were apparently colorblind (table 6). Now that we know about the stochastic somatic events that appear to be involved both in lyonization and in the process of forming MZ twin embryos (Nance 1990), no one would interpret the failure of such twin pairs to be concordant as an indication that Duchenne dystrophy, for example, is in some cases an environmental rather than a genetic disease. The point I am trying to make is that, when we find discordance in MZ twins for a trait that for some other reason we really believe is genetic, perhaps we should at least consider the possibility that genetic events in the somatic cells may contribute to the expression of the trait and possibly to the observed discordance in MZ twins. Other than cancer, what are my candidates for such diseases? We know that somatic rearrangements are extensively involved in the immune response, so that it seems to me that any disease that involves an autoimmune component, such as IDDM, might be expected to exhibit a less than 100% concordance rate in MZ twins. Surely, the higher concordance rate for diabetes that is observed among MZ twins who carry a high-risk HLA haplotype cannot mean that those pairs are more often concordantly exposed to cow's milk or some other environmental factor. Instead, it seems likely that the range of stochastic events, in a suitably provoked immune system, that will elicit an autoimmune response is greatly increased in the presence of specific high-risk HLA haplotypes. I am grateful to my daughter, Dr. Martha Nance, in Minneapolis for pointing out to me that narcolepsy is another disease for which MZ twins are often discordant despite the fact that it is clearly familial in some cases and shows striking HLA associations (Guilleminault et al. 1989; Pollmacher et al. 1990). Finally, one cannot help but wonder whether the frequently reported discordance in MZ twins for Alzheimer disease (Nee et al. 1987) and possibly schizophrenia and other affective psychoses will be explained in part by either acquired differences

Table 6

Discordant Expression of X-linked Traits in Female MZ Twins

Condition	Reference
Colorblindness	Nettleship 1912
Dyschromatopsia	Walls and Mathews 1952
Colorblindness	Zanen and Meunier 1958
Colorblindness (Dionne quintuplets)	Waardenburg 1963, p. 1476
Deuteranomaly	Jørgensen et al. 1992
Duchenne dystrophy	Burn et al. 1986
Duchenne dystrophy	Chutkow et al. 1987
Duchenne dystrophy	Pena et al. 1987
Duchenne dystrophy	Bonilla et al. 1990
Duchenne dystrophy	Richards et al. 1990
Duchenne dystrophy	Lupski et al. 1991
G6PD deficiency	Phelan et al. 1980
Kallmann syndrome	Hermanussen and Sippell 1985
Factor IX deficiency	Kitchens 1987
Fragile X syndrome	Jenkins et al. 1992
Hunter disease	Winchester 1992

in brain structure or possibly by somatic changes in nuclear or mitochondrial genes. These ideas have important potential implications. To the extent that diseases result from interactions between high-risk genotypes and either identifiable or stochastic environmental factors, perhaps our research efforts would be better served by focusing more on the identification and monitoring of high-risk individuals as a therapeutic strategy. Our final trip back to the future begins in China almost 100 years ago, where we will find an answer to a final question.

What Do Clipper Ships Have to Do with Global Education in Genetics?

When I was preparing this talk, most of my colleagues advised me to stick to science, and that is what I have tried to do. However, I cannot resist the opportunity to tell you about one final trip I recently took back to the past, because of the implications it has for the future of our society. This spring, I had an opportunity to visit Shanghai, China, for the first time in 50 years. My grandfather was a Greek and Latin scholar who went to China as an educational missionary before the turn of the century. My father received his elementary and secondary education from his mother and returned to Shanghai in the early 1930s to practice surgery after completing his undergraduate and medical education at Vanderbilt University. My hosts in Shanghai helped me find the houses where my family and I used to live. They took me through my grandfather's home at the university he helped to found in Souchow; they showed me the Pavilion of Benevolent Longevity that was constructed in his honor on the occasion of his 80th birthday, and they introduced me to retired professors who were once his students. When my hosts learned that I was president of your society, they also arranged for me to visit and talk at several medical schools and universities in the Shanghai area. As I was about to begin my first lecture, I was profoundly moved by the realization that my grandfather had first arrived in Shanghai on a clipper ship almost exactly 100 years earlier and that my audience included graduates of the university that he had helped to found and later served as president. After I returned home, I decided to send my hosts subscriptions to our *Journal,* as an expression of my appreciation. When I casually inquired of our business office how many subscribers we have in mainland China, I was astonished to learn that, in that country of 1 billion people, there are only two who subscribe to what we like to think is the world's leading journal of human genetics. This experience has convinced me that, during the last decade of this century, our society has a historic opportunity and perhaps even an obligation to help scientists in countries like China and the emerging Eastern Bloc nations become full partners in the scientific community. This is not a new idea, but, unless you are actually confronted by the need, it is easy to overlook, and I would invite you all to try to think of and act on effective ways in which this goal can be achieved.

The first meeting of this society that I attended was held in New York in 1963. Dr. James F. Crow was president that year and gave a talk on genetic load theory. It was a very large meeting, for the time, that included at least 200 geneticists, and I clearly remember hearing a nervous postdoctoral student giving his first scientific presentation on "New Haptoglobin Alleles: A Prediction Confirmed." As I finish this address, I am very much aware that someone in this audience, possibly someone who is attending our meeting for the first time, may well be the person who will be giving the Presidential Address in the year 2022 and attempting to relate the research they are doing now, to whatever it is that human geneticists will be most interested in then. Whoever that person may be, I hope very much that you have as much fun as I have had going back to your future.

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